

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
22 November 2001 (22.11.2001)

PCT

(10) International Publication Number
WO 01/088188 A3(51) International Patent Classification⁷: **C12Q 1/68,**
G06F 19/00

(21) International Application Number: PCT/JP01/04192

(22) International Filing Date: 18 May 2001 (18.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000-145977 18 May 2000 (18.05.2000) JP(71) Applicant (for all designated States except US): **NIHON UNIVERSITY, SCHOOL JURIDICAL PERSON**
[JP/JP]; 8-24, Kudan-minami 4-chome, Chiyoda-ku, Tokyo 102-8275 (JP).

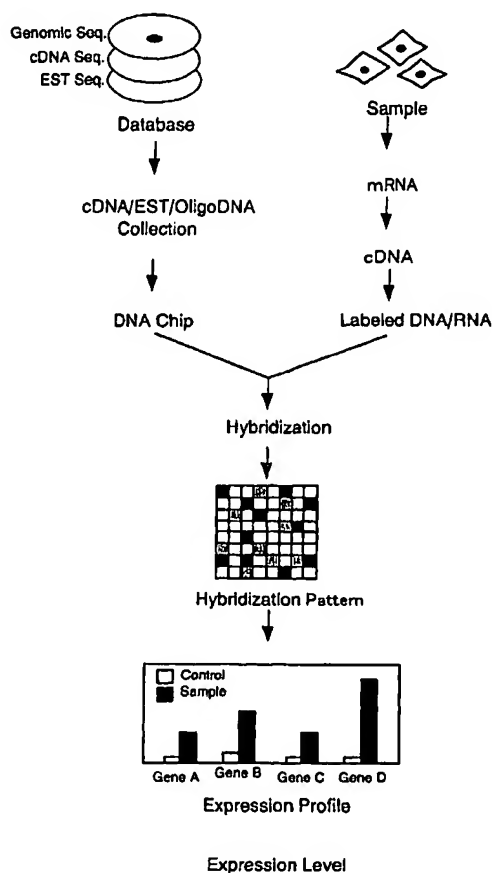
(72) Inventors; and

(75) Inventors/Applicants (for US only): **ISHIKAWA, Koichi**[JP/JP]; 28-32-1304, Hongo 1-chome, Bunkyo-ku, Tokyo 113-0033 (JP). **ASAI, Satoshi** [JP/JP]; 36-10-1106, Higashi-ohizumi 1-chome, Nerima-ku, Tokyo 178-0063 (JP). **TAKAHASHI, Yasuo** [JP/JP]; 3-8-405, Mukaihara 2-chome, Itabashi-ku, Tokyo 173-0036 (JP). **NAGATA, Toshihito** [JP/JP]; 52-2-205, Ohyaguchi-kamicho, Itabashi-ku, Tokyo 173-0032 (JP). **ISHII, Yukimoto** [JP/JP]; 22-10, Sekibara 2-chome, Adachi-ku, Tokyo 123-0852 (JP).(74) Agents: **HIRAKI, Yusuke** et al.; Toranomon No.5 Mori Building Third Floor, 17-1, Toranomon 1-chome, Minato-ku, Tokyo 105-0001 (JP).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,

[Continued on next page]

(54) Title: METHOD FOR EXAMINING ISCHEMIC CONDITIONS



(57) Abstract: The present invention provides a method for examining ischemic conditions, comprising measuring the expression levels of particular genes in a test sample or determining the expression profile of a gene group in the sample comprising a plurality of genes selected from said particular genes.



SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

Published:

— with international search report

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
12 June 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/04192

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12Q1/68 G06F19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, SEQUENCE SEARCH, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--------------------------------|
| X | LYN DEBORAH ET AL: "Gene expression profile in mouse myocardium after ischemia." PHYSIOLOGICAL GENOMICS, vol. 2, May 2000 (2000-05), pages 93-100, XP002222392 May, 2000 | 1,3-5,8, 10,11, 13,14,16 |
| Y | ISSN: 1094-8341 the whole document | 2,6,7,9, 12,15 |
| | --- | -/-- |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 November 2002

Date of mailing of the international search report

28. 02. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Aguilera, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/04192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--------------------------------|
| X | NAGATA TOSHIHITO ET AL: "Monitoring of expression of genes using high-density oligonucleotide DNA array (GeneChip™, Affymetrix) during ischemia-reperfusion in mouse hippocampus." JAPANESE JOURNAL OF PHARMACOLOGY, vol. 82, no. Suppl. 1, 2000, page 106P XP002222393 73rd Annual Meeting of the Japanese Pharmacological Society.;Yokohama, Japan; March 23-25, 2000 ISSN: 0021-5198 | 1,3-5,8, 10,11, 13,14,16 |
| Y | abstract | 2,6,7,9, 12,15 |
| X | --- SORIANO M A ET AL: "Changes in temporal expression of genes, monitored using oligonucleotide probe arrays, in an animal model of focal ischemia." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-86.1, XP002222394 30th Annual Meeting of the Society of Neuroscience;New Orleans, LA, USA; November 04-09, 2000 ISSN: 0190-5295 | 1,3-5,8, 10,11, 13,14,16 |
| Y | abstract | 2,6,7,9, 12,15 |
| Y | --- MOROOKA HIROAKI ET AL: "Ischemia and reperfusion enhance ATF-2 and c-jun binding to cAMP response elements and to an AP-1 binding site from the c-jun promoter." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 50, 1995, pages 30084-30092, XP002222395 ISSN: 0021-9258 the whole document | 2,6,7,9, 12,15 |
| Y | --- KNIGHT RICHARD J ET AL: "Stimulation of c-Jun kinase and mitogen-activated protein kinase by ischemia and reperfusion in the perfused rat heart." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 218, no. 1, 1996, pages 83-88, XP002222396 ISSN: 0006-291X Abstract, Introduction --- | 2,6,7,9, 12,15 |

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/04192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P,X | WO 01 27624 A (SUPERARRAY INC) 19 April 2001 (2001-04-19) page 43, line 1 -page 46, line 32 page 52, line 15 -page 53, line 4 table 2 ----- | 1-16 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 01/04192

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-16 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-16 (ALL PARTIALLY)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-16 (all partially)

Methods of examining ischemic conditions and methods of screening for ischemic condition-improving drugs, comprising measuring in a test sample the expression levels of genes having the nucleotide sequence of SEQ ID NO: 1, or genes encoding the amino acid sequence of SEQ ID NO 1. DNA chip comprising said genes, and computer-readable media in which expression level of said genes, or instructions to measure and compare expression levels of said genes, is recorded.

2. Claims: 1-16 (all partially)

Methods of examining ischemic conditions and methods of screening for ischemic condition-improving drugs, comprising measuring in a test sample the expression levels of genes having the nucleotide sequence of SEQ ID NO: 2, or genes encoding the amino acid sequence of SEQ ID NO: 2. DNA chip comprising said genes, and computer-readable media in which expression level of said genes, or instructions to measure and compare expression levels of said genes, is recorded.

[idem for SEQ ID NOs: 3-1066]

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1-16 (all partially)

Present claims 2, 6, 7, 9, 12 and 15 relate to methods and products by reference to a desirable characteristic or property, namely being "functionally equal" to the genes listed in the application. The claims cover all methods and products having this characteristic or property, whereas the application provides support within the meaning of PCT Article 6 and disclosure within the meaning of PCT Article 5 for only a limited number of such methods and products, i.e. those using or having sequences SEQ ID NO: 1.

On the other hand, the lack of a precise definition of said "functionally equal" genes, either in terms of sequence or in terms of specific detailed function, renders the scope of the claims unclear within the meaning of PCT Article 6.

In the present case, the lack of clarity, support and disclosure is such that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been limited to those parts of said claims which appear to be clear, supported and disclosed, namely the methods and probes using genes having sequence of SEQ ID NO: 1, or genes encoding the amino acid sequences of SEQ ID NO: 1 (see also form PCT/ISA/206, Invitation to pay additional fees).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 01/04192

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date | |
|---|---------------------|----------------------------|---------------------|------------|
| WO 0127624 | A | 19-04-2001 | AU 1630501 A | 23-04-2001 |
| | | | EP 1224463 A2 | 24-07-2002 |
| | | | WO 0127624 A2 | 19-04-2001 |
| ----- | | | | |